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CLINICAL REVIEW

Obstructive sleep apnea and asthma: Associations and treatment implications

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SUMMARY

Obstructive sleep apnea (OSA) and asthma are highly prevalent respiratory disorders and are frequently co-morbid. Risk factors common to the two diseases include obesity, rhinitis, and gastroesophageal reflux (GER). Observational and experimental evidence implicates airways and systemic inflammation, neuromechanical effects of recurrent upper airway collapse, and asthma-controlling medications (corticosteroids) as additional explanatory factors. Therefore, undiagnosed or inadequately treated OSA may adversely affect control of asthma and vice versa. It is important for clinicians to be vigilant and specifically address weight-control, nasal obstruction, and GER in these populations. Utilizing validated screening instruments to affirm high risk of co-morbid OSA or asthma in persistently symptomatic patients will allow clinicians to cost-effectively test and treat appropriate patients, potentially improving outcomes. While non-invasive ventilation in acute asthma improves outcomes, the role of chronic continuous positive airway pressure (CPAP; the first-line treatment for OSA) in improving long-term asthma control is not known. Future research should focus on the impact of optimal CPAP therapy and adherence on asthma symptoms and outcomes.

Introduction

Obstructive sleep apnea (OSA) and asthma are highly prevalent chronic respiratory disorders that share several risk factors for disease expression and progression. Both symptoms of OSA and diagnosed OSA are more frequent in clinical populations with asthma compared to other populations.[1–3] In addition to overlapping risk factors, multiple evidence-based and hypothetical mechanisms have been postulated to explain the frequent co-existence of OSA and asthma, also referred to as the "alternative overlap syndrome".[4–6] However, the effects of the direct pathophysiologic consequences of OSA (e.g., chronic intermittent hypoxemia, circadian alteration of autonomic functions, and increased intrathoracic pressure swings related to the occluded upper airway) on the clinical severity of asthma are poorly understood. Similarly, the impact of continuous positive airway pressure (CPAP), a first-line treatment of OSA, on asthma symptoms and quality of life remain unclear.

Here we discuss the epidemiologic and mechanistic evidence supporting the association of OSA with asthma in adults, with emphasis on studies published in the last five years and those examining the effects of standard therapies for OSA on asthma outcomes.

Epidemiologic studies of OSA and asthma overlap

The prevalence of OSA in the adults is estimated at 2–4% in the general population.[7] Several studies have described the prevalence of OSA based on snoring, validated screening questionnaires, and objective tests such as polysomnography in populations with allergic airways disease, nocturnal asthma, and severe or poorly-controlled asthma. In a general population European study, a 17% prevalence of snoring and 14% of witnessed apneas was reported in those with physician-diagnosed asthma, compared to an overall prevalence of 10% and 7% respectively.[8] While population-based studies utilizing polysomnography to identify the prevalence and severity of OSA in asthmatics have not been reported, several studies have examined clinical populations with asthma. Recent

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Table 1
Selected studies on the association of OSA and asthma published in the last five years.

Study/year	Study design/sample (n)	Measurement of OSA and asthma	Result
Bhattacharya et al., 2012[101]	Cross-sectional/adult OSA related office visits to otorhinolaryngologist (4.1 ± 1.2 million visits)	OSA and asthma: International Classification of Diseases, Ninth Revision (ICD-9) codes	Increased risk for asthma (*OR 2.7; CI 1.6, 4.6) in OSA
Teodorescu et al., 2012[64]	Cross-sectional/adult asthma referral population (752)	OSA: SA-SDQ Asthma: frequency of daytime and nighttime symptoms (NAEPP classification)	Increased OSA risk with persistent daytime (OR 1.9; CI 1.3, 2.9) and nighttime (*OR 1.9; CI 1.3, 2.9) symptoms of asthma
Williams et al., 2011[102]	Cross-sectional/women before and during pregnancy (1335)	OSA: habitual snoring Asthma: self-report of physician-diagnosed asthma	Increased OSA risk in asthmatics both before (*OR 2.1; CI 1.1, 4.1) and during (*OR 1.79; CI 1.1, 3) pregnancy
Teodorescu et al., 2010[2]	Cross-sectional/adult asthma referral population (472)	OSA: SA-SDQ Asthma control questionnaire (ACQ)	Asthmatics at high risk for OSA had increased risk for poorly-controlled asthma (*OR 2.9; CI 1.5, 5.3)
Alharbi et al., 2009[9]	Cross-sectional/OSA referral population (606)	OSA: AHI > 5/hour on PSG Asthma: self-report of physician-diagnosed asthma	35% prevalence of asthma, body mass index (BMI) was a significant predictor (*OR 2.1; CI: 1.7, 2.4)
Teodorescu et al., 2009[13]	Cross-sectional/asthma referral population (244)	OSA: SA-SDQ Asthma: symptoms (NAEPP classification)	Predictors of high OSA risk in asthma were female gender (*OR 2.1; CI: 1.1, 4.0), asthma severity (*OR 1.6; CI: 1.2, 2.0), GERD (*OR 2.7; CI: 1.5, 4.8), use of ICS (*OR 4.0; CI: 1.5, 10.5)
Auckley et al., 2008[1]	Cross-sectional/asthma clinic population (177) vs. general medicine clinic population (GMC; 328)	OSA: Berlin sleep questionnaire Asthma: pulmonologist diagnosed, severity assessed by spirometry GMC: participants with history of OSA and asthma excluded	High OSA risk was more prevalent in asthma vs. GMC population (39.5% vs. 27.2%, $^{@}p = 0.004$)

Abbreviations: AHI = apnea hypopnea index, CI = 95% confidence interval, GERD = gastroesophageal reflux, GMC = general medicine clinic, ICS = inhaled corticosteroids, NAEPP = National Asthma Education and Prevention Program, OSA = obstructive sleep apnea, OR = unadjusted odds ratio, PSG = polysomnography, SA-SDQ = sleep apnea scale of the sleep disorders questionnaire, *OR = adjusted odds ratio, $^{\#}p$ = adjusted p-value, $^{@}p$ = unadjusted p-value.

observational and prospective studies examining the risk of OSA in asthma are summarized in Table 1. Overall, the risk of OSA appears to be approximately doubled in asthmatic populations and asthma severity, female gender, obesity, and gastroesophageal reflux (GER) are important positive moderators of this risk. Conversely, a third of clinical populations with OSA report physician-diagnosed asthma.[9]

Potential mechanisms of increased OSA risk in asthma

Asthma is a chronic inflammatory disease associated with variable airflow obstruction and bronchial hyper-responsiveness.[10] The relationship of chronic airway inflammation to the clinical symptoms of asthma (wheezing, dyspnea, and cough) has been well described.[10] However, our knowledge is limited regarding the impact of asthmatic airway inflammation on the development or worsening of OSA. The persistent airway mucosal inflammation that occurs in asthma can promote a reduction in the surface area of the airways, including the upper airway. This has been demonstrated by Collett and colleagues who used radiographic techniques to reveal a decrease in the cross-sectional area of the pharynx in asthmatics during bronchoprovocation testing.[11] This reduction of surface area of the pharynx provides a prime setting for the development of OSA. Additionally, the medications used to reduce airway inflammation in asthma can promote OSA. Yigla et al. found that asthmatics chronically on oral corticosteroids (OCS) or requiring frequent bursts of OCS had a very high (95%) prevalence of OSA.[12] This high prevalence may be explained by the multiple effects OCS have on the upper airway including parapharyngeal fat deposition and myopathy which can lead to an increase in upper airway collapsibility. It has also been hypothesized that exogenous steroid induced metabolic-alkalosis may induce a propensity for hypoventilation.[4] Whether the same effects occur with inhaled corticosteroids (ICS) are not clear though laryngeal muscle dysfunction has been reported with the use of ICS and a recent study showed an increased risk of OSA with ICS use in a dose-dependent manner.[13,14] Other factors in addition to corticosteroid therapy must also contribute to this high prevalence of OSA in difficult to control asthma, as even in persons with Cushing's disease (hypercortisolism), the prevalence of OSA is lower at 50%.[12] Nocturnal worsening of asthma is a well-described phenomenon and multiple factors contribute including nocturnal GER, a decrease in beta-receptor density at night leading to an alteration in autonomic tone and circadian variations in cytokine and hormone secretion.[15] Regardless of the etiology of nocturnal asthma, it can lead to chronic sleep fragmentation, which promotes upper airway collapsibility.

Other co-morbid conditions that are closely associated with asthma may have a strong influence on the development of OSA including rhinitis, obesity, and GER, as illustrated in Fig. 1. These co-morbid conditions have been shown to cause airway inflammation and in some cases bronchial hyperactivity.

Rhinitis

The vast majority of patients with asthma have rhinitis (allergic and non-allergic).[16] Patients with severe allergic rhinitis have been shown to have a higher prevalence of snoring with and without daytime sleepiness (6% and 46%, respectively), compared to controls (0.5% and 27%, respectively).[17] Conversely, Canova and colleagues found higher rates (11% vs. 2.5%) of allergic rhinitis in OSA subjects compared to chronic obstructive pulmonary disease subjects.[18] Rhinitis and nasal obstruction cause changes in airflow velocity and resistance, effectively increasing negative pressure in the upper airway during inspiration.[19] This promotes upper airway collapse and symptoms of sleep-disordered breathing including snoring and apnea.[20,21] This concept has been demonstrated in a study of allergic and non-allergic rhinitis patients, in whom both forms of rhinitis were shown to be risk factors for a high apnea–hypopnea index.[22] However, the degree of nasal obstruction does not directly correlate with the severity of sleep-disordered breathing.[23] Further, in patients with allergic rhinitis,

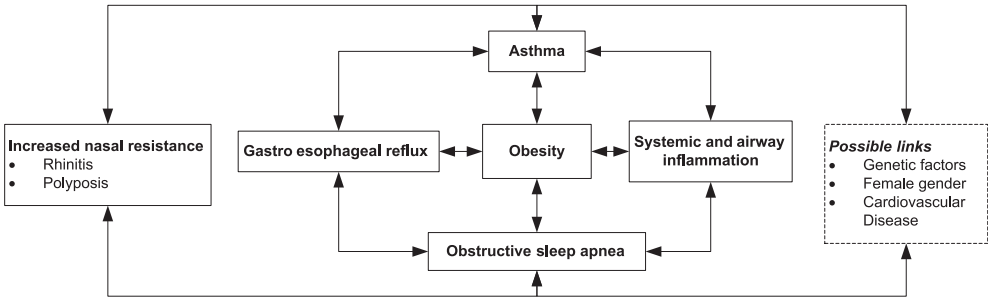

Fig. 1. Obstructive sleep apnea and asthma: pathophysiologic links.

circadian rhythms can lead to a peak in nasal congestion during the early morning hours, possibly potentiating the expression of OSA.[24]

Obesity

Obesity is the strongest risk factor for OSA and may affect breathing in several ways, including a change in structure or function (collapsibility) of the upper airway, reductions in functional residual capacity, an increase in oxygen demand, and a change in the respiratory drive and load compensation relationship.[25–27] Additionally, obesity has been associated with the generation of pro-inflammatory mediators such as leptin and other adipokines.[28] These inflammatory mediators cause a low-grade systemic inflammation and generate airway inflammation independently of co-existing airway disease.[29,30] Obesity is an independent risk factor for asthma and a dose–response effect of increasing body mass index (BMI) on increasing risk of incident asthma has been shown.[31–33] The odds appear to be approximately two fold higher in women.[34,35] Obese asthmatics are more likely to experience poorer control of asthma and an inferior quality of life compared to non-obese asthmatics.[36,37] Studies have demonstrated that obesity may follow the development of asthma.[38] The use of oral corticosteroids, daytime fatigue caused by poor sleep and less than optimal asthma control (poor exercise tolerance) can all promote obesity in asthmatics. Obese asthmatics exhibit certain unique characteristics, such as absence of eosinophil dominant inflammation and relative glucocorticoid resistance, which may confound the diagnosis and evaluation of response to therapy in asthma.[39]

Gastroesophageal reflux (GER)

A recent prospective study demonstrates a higher incidence of asthma (symptoms and physician diagnosis) and OSA (symptoms) in a general population sample with persistent GER, after adjusting for BMI.[40] Self-reported GER occurs in as high as 80% asthmatics, while GER identified by a positive pH probe is reported at a rate of 38%.[41] While reasons for increased prevalence of GER in asthma are not clear, one hypothesis is the increased transdiaphragmatic pressure gradient promotes acid reflux into the esophagus.[41] Microaspiration of gastric acid in turn exacerbates bronchoconstriction and airway inflammation, thereby predisposing to respiratory symptoms and asthma.[42] Second, bronchospasm may be induced by a vagal reflex, triggered by gastric acid in the distal esophagus that leads to an increase in respiratory resistance and "priming" of the airways for bronchoconstriction.[41] Though both these hypotheses are plausible and have been shown to occur in animal models of asthma, they have not been adequately tested in humans. In addition, commonly used asthma medications, (i.e., beta-adrenergic agonists and theophylline), may reduce the lower esophageal sphincter tone and, promote GER in asthmatics. OSA patients are more likely to have nocturnal GER, which is a well-known trigger for nocturnal asthma and is considered to be more harmful than daytime GER.[43,44] Emilsson and colleagues have hypothesized that the repeated stress of negative intrathoracic pressure caused by OSA leads to intermittent loss of lower esophageal sphincter tone, worsening nocturnal GER.[40] Additionally, nocturnal GER can cause arousal during sleep leading to sleep fragmentation and upper airway edema promoting the expression of OSA. These observations demonstrate a bi-directional association of GER with asthma and OSA.[45,46]

Potential effects of pathophysiologic consequences of OSA on asthma

Direct adverse effects of repeated upper airway collapse during sleep in OSA include exaggerated intrathoracic pressure changes, chronic intermittent hypoxia, and sleep fragmentation. Here we discuss how these changes directly and through intermediate pathways moderate the expression of asthma.

Neuromechanical effects of upper airway collapse

Upper airway collapse, partial or complete, is pathognomonic of OSA. Snoring can evoke vibration frequencies that cause soft-tissue damage in the upper airway and nasal passages.[47] Tissue obtained from patients undergoing surgical treatments for OSA have revealed marked subepithelial edema, excessive plasma cell infiltration, and a reduction of the tethering of epithelium to connective tissue papillae.[47] In the nasal lavage fluid of OSA patients, increased numbers of polymorphonuclear leukocytes and high concentrations of bradykinin and vasoactive intestinal peptide have been found.[48,49] Increased expression of cysteinyl leukotriene receptors (LTR-1, LTR-2) occurs, predominantly in the epithelial layer of the tonsillar parenchyma, affected by the vibration trauma of OSA.[50] The cysteinyl leukotrienes are major mediators of inflammation and have potent bronchoconstrictive activity, increase microvasculature permeability, mucus secretion, and eosinophil recruitment. Inflammatory and denervation changes affect not only the mucosa, but also alter upper airway muscle fibers.[51] Considering the continuity of the upper and lower airways, it is plausible that these changes may trigger or exacerbate asthma.

In addition to the mechanical trauma resulting in local inflammation, the repeated stimulation of the oropharynx and glottis inlet or larynx as well as the repetitive Müller maneuvers (inspiratory effort against a closed glottis), can stimulate potent neural reflexes.[52] The increased transdiaphragmatic pressure gradient is likely transmitted to the entire respiratory system, causing bronchial inflammation and activation of the neural receptors by pro-

inflammatory neuropeptides and peptides leading to reflex bronchoconstriction.[53] Furthermore, the increase in vagal tone that occurs during apneic episodes stimulates muscarinic receptors in the central airway which results in bronchoconstriction and nocturnal asthma symptoms.[5] The markedly negative intrathoracic pressures may exaggerate nocturnal pulmonary blood pooling, which has been associated with nocturnal asthma.[54] Supine position, which increases upper airway collapsibility, has also been shown to increase bronchial hyperesponsiveness.[55]

Chronic intermittent hypoxia

Another trigger for bronchial hyperreactivity in OSA is the intermittent oxygen desaturation resulting from airflow cessation. Several animal studies have found that even mild hypoxia can enhance the bronchial responsiveness to methacholine and histamine.[5] Denjean and colleagues demonstrated this concept in mild asthmatics and found in subjects that experienced isocapnic hypoxia, there was an increase in bronchial responsiveness to methacholine.[56] The airway hyperresponsiveness seen after hypoxia exposure is likely mediated through vagal pathways, initiated by stimulation of carotid body receptors.[57]

Both airway (upper and lower) and systemic inflammation exist in individuals with OSA. Carpagnano and colleagues recently reviewed the use of non-invasive methods; induced sputum (IS) and exhaled breath condensate (EBC) in measuring airway inflammation in patients with OSA.[28] Evidence of airway inflammation in OSA has been demonstrated by increased inflammatory markers including sputum cysteinyl leukotriene levels, tumor necrosis factor-α (TNF-α), exhaled nitric oxide, pentane and 8-isoprostane.[58] These inflammatory and oxidative markers are derived from reactive oxygen species (ROS) that are produced in response to episodic hypoxia.[59] Many of these inflammatory mediators, such as TNF-α, vascular endothelial growth factor (VEGF), and 8-isoprostane, have been found to correlate with OSA severity.[31]

Airway neutrophilia is a prominent feature found in the IS of OSA patients and correlates with the apnea–hypopnea index (AHI).[49,53,60] The reason for this finding is not clear, but other phenotypes associated with airway neutrophilia are obese asthmatics, older asthmatics, and those with uncontrolled GERD.[61–63] Additional mechanisms that may account for the airway neutrophilia in OSA are intermittent hypoxia and upper airway trauma. The intermittent hypoxia can induce changes in leukocyte function in animal models. The change in leukocyte function includes an increase in the production of 5-lipoxygenase (5-LPO) by airway neutrophils, which triggers the production of LTB4, a strong chemoattractant of neutrophils.[28,47] Other non-invasive methods, such as nasal lavage fluid, have shown higher concentrations of bradykinin and vasoactive intestinal peptide in OSA subjects compared to BMI-matched controls.[64]

In addition, chronic systemic inflammation can contribute to the airway inflammation present in OSA and can cause an increase in bronchial hyperresponsiveness and a loss of asthma control.[30] The systemic inflammation that exists in OSA appears to be low-grade and is characterized by the elevation of serum pro-inflammatory cytokines and chemokines such as TNF-α, C-reactive protein (CRP), and interleukin-6 (IL-6) as compared to nonapneic obese controls and hypersomniacs.[65,66] The postulated mechanisms of this systemic inflammation are many. One contributing factor to this state of low-grade systemic inflammation is obesity. The pro-inflammatory mediators IL-6 and TNF-α are synthesized by visceral adipose cells which are often more prominent in the obesity that exists with OSA. This mix of pro-inflammatory cytokines may promote other pro-inflammatory processes including leukocyte recruitment via endothelial activation and enhancement of resident airway cell (epithelial cells, mast cells and fibroblasts) activation.[5] Other mechanisms include a TNF-α polymorphism (−308A) that increases TNF-α production and has been associated with OSA.[67] As discussed above, the intermittent hypoxia that occurs in OSA can cause the production of ROS. These ROS may trigger inflammatory pathways through signaling of the transcription factors, nuclear factor-κB (NF-κB) and activator protein 1.[68] Evidence of increased levels of NF-κB in neutrophils and monocytes has been found in OSA subjects and correlates with disease severity.[69] Furthermore, OSA has been associated with prothrombotic factors, such as fibrinogen, which are important in the development of inflammatory diseases.[70] A decrease in fibrinolytic activity and an elevation in fibrinogen, D-dimer, α1-antitrypsin, high sensitive C-reactive protein, and pro-BNP levels have been found in OSA patients compared to control subjects.[71] In this study by Sariman et al., fibrinogen, pro-BNP and D-dimer levels were shown to positively correlate with duration of nocturnal oxygen desaturation. An emerging hypothesis unifying OSA and asthma involves leptin, an adipokine which is upregulated in patients with OSA via centripetal obesity[72,73] and possibly through obesity-independent pathways such as chronic intermittent hypoxia.[74,75] Leptin exerts systemic pro-inflammatory effects (on adipocytes and hematopoietic cells) and has a key immune modulating role within the respiratory system.[76] Therefore, elevated leptin levels and a relative resistance to leptin may play an important mediating role in the overlap of OSA and asthma.

Together, these data demonstrate that airway and systemic inflammation consequent to obesity and intermittent hypoxia occurs in OSA and adversely impacts asthma control.

Sleep fragmentation

OSA leads to sleep fragmentation with repeated arousals, which is associated with heightened sympathetic activity, activation of the

Table 2
Studies examining role of continuous positive airway pressure treatment in adult asthma.

Study/year	Phenotype of asthma/OSA/sample (n)	Intervention/control	Result
Busk et al., 2013[32]	Stable asthma *at low risk** *for* OSA, $n = 25$	1 wk of 8–10 cm H_2O CPAP/sham CPAP	$\Delta\log PC_{20}$ on MCT increased on CPAP vs. sham CPAP (+0.41; $p < 0.04$).
Korczynski et al., 2009[98]	Severe# OSA *without* asthma, $n = 101$	3 wk of CPAP/no treatment	$\Delta\log PC_{20}$ on MCT decreased with CPAP (1.38 ± 0.30 to 1.26 ± 0.50, $p = <0.05$) compared to no change in control group.
Lafond et al., 2007[103]	Stable asthma with severe# OSA, $n = 20$	6 wk of CPAP/no control	No change in ΔPC_{20} and ΔFEV1, quality of life specific to asthma and OSA improved ($p \leq 0.001$).
Ciftci et al., 2005[104]	Nocturnal asthma with moderate to severe# OSA, $n = 16$	2 mo of CPAP/no control	No change in PFT, improvement in nighttime asthma symptoms@ ($p < 0.05$).

Abbreviations: CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, MCT = methacholine challenge test, PC_{20} = the methacholine concentration that decreased forced expiratory volume in 1 s (FEV1) by 20%, * = risk defined by Berlin sleep questionnaire, # = severity of OSA defined by apnea hypopnea index on polysomnography, PFT = pulmonary function test, @ = Global Initiative for Asthma (GINA) guidelines.

cardiac conduction system, and nocturnal surges in blood pressure.[77,78] Although, unstable neural respiratory drive has been linked to nocturnal asthma, the direct effects of sleep fragmentation on expression of asthma remains to be investigated.[79] Hypothetical mechanisms by which sleep fragmentation may worsen asthma control include left ventricular dysfunction, impaired immunological function, and weight gain.[80–83]

Overlap of OSA and asthma: implications for treatment

Based on the preceding discussion, it is reasonable to expect an effective therapy for OSA to favorably impact subjective and objective asthma control and vice versa. Early studies examined the role of non-invasive ventilation (NIV) in acute respiratory failure secondary to asthma and reported improvements in gas exchange and reduction in rates of mechanical ventilation.[84,85] However, the role of NIV in severe acute asthma remains controversial.[86] Another recent report suggests that CPAP may be useful as a controlled oxygen delivery modality for acute respiratory failure (including asthma) in the prehospital setting.[87]

The first-line treatment for OSA in adults is nasal CPAP. A purely mechanical effect of CPAP is a sustained increase in functional residual capacity (FRC), which may reduce airway smooth muscle contractility.[88,89] CPAP effectively reduces GERD and inflammation OSA patients and thus may favorably impact asthma control.[90–93]

It is important to emphasize that examination of the role of CPAP in asthma is complicated by the multitude of pathways in addition to recurrent upper airway collapse that mediate the OSA–asthma overlap, including obesity, rhinitis with reduced nasal patency, and GER. Nevertheless, based on promising animal data,[94,95] few studies have examined the role of CPAP in different phenotypes of asthma and OSA, with variable results. Of these, selected recent prospective studies are summarized in Table 2. Additional studies have been reviewed and published recently.[96] Notably, it appears that CPAP may increase bronchial hyperresponsiveness in non-asthmatics with OSA[97,98] and lead to objective degradation of sleep architecture in asthmatics without OSA.[99] Given these contradictory results in different clinical populations, larger prospective studies on well-defined phenotypes of asthma and OSA are needed to clarify the role and limitations of CPAP in patients with these two common respiratory disorders.

The role of second line treatments for OSA, mandibular advancement devices (MAD), ear, nose, and throat (ENT) and bariatric surgeries have not been prospectively examined for outcomes in populations with asthma overlap. A large prospective series, reported high prevalence of asthma and OSA (approximately one third each) in a morbidly obese bariatric referral population, but no overlap of the two disorders. This study also found significant improvement in asthma and nearly complete resolution of OSA, two years after surgery.[100] Similarly, asthma-controlling medications (e.g., corticosteroids, leukotriene antagonists) and less conventional treatment options such as immunotherapy, biological drugs like monoclonal antibodies, tumor necrosis factor-α blockers and oligonucleotides, phosphodiesterase inhibitors, antimicrobials and bronchial thermoplasty have not been tested in populations with OSA–asthma overlap.

Considering the current evidence-base, which is limited by the small sample size and the heterogeneity of the clinical populations studied, it remains difficult to draw firm conclusions or inform clinical practice regarding optimal management strategies in patients with OSA–asthma overlap. However, a careful evaluation for exacerbating co-morbidity,[4] in addition to optimizing treatment of both OSA and asthma remains crucial in this population.

Practice points

1) Obstructive sleep apnea (OSA) and asthma are highly prevalent respiratory disorders that frequently overlap in patients.
2) A high index of suspicion is warranted for overlap of OSA and asthma, particularly in the presence of obesity, rhinitis, gastroesophageal reflux (GER), and in patients poorly responsive to therapy.
3) Individualized therapy addressing moderating factors such as weight gain, GERD, nasal obstruction, and cardiovascular disease is warranted for optimal outcomes.

Research agenda

1) Identify phenotypes and genetic factors in OSA–asthma overlap at high-risk for adverse health outcomes.
2) Examine the role and limitations of standard therapies for OSA and asthma in improving health outcomes in patients with OSA–asthma overlap.
3) Identify and prospectively test biomarkers appropriate for clinical use, which predict risk and treatment outcomes in patients with OSA–asthma overlap.

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